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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 295 656 B1**

B5

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **11.11.92**

(51) Int. Cl.5: **C07D 277/82**, C07D 277/84, C07D 417/04, C07D 417/12, C07D 513/04, A61K 31/425, A61K 31/435, A61K 31/635

(21) Application number: **88109552.5**

(22) Date of filing: **15.06.88**

(54) Benzothiazole derivative, its use, and pharmaceutical compositions comprising it.

(30) Priority: **17.06.87 JP 150987/87**

(43) Date of publication of application:
21.12.88 Bulletin 88/51

(45) Publication of the grant of the patent:
11.11.92 Bulletin 92/46

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 003 141
DE-C- 927 507
GB-A- 808 191
GB-A- 1 538 822
US-A- 4 006 242
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Description

The present invention relates to a benzothiazole derivative which exhibits excellent pharmaceutical activities.

[Prior Art]

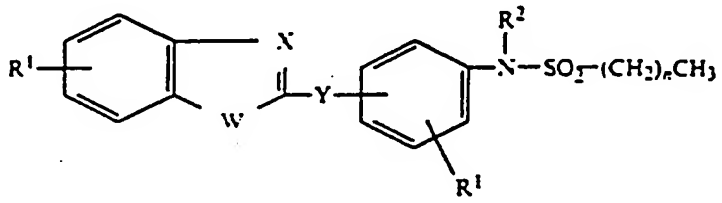
Asthmatic attack occurs as a result of a complicated combination of vital reactions. It is generally believed that the asthmatic attack is mainly due to stenosis of the air passage caused by various chemical mediators which are produced and liberated by an antigen-antibody reaction as a trigger.

Examples of known chemical mediators include histamine, prostaglandin, and SRS-A. Among them, SRA-A was proved to be leukotrienes C_4 and D_4 in 1979 by Professor Samuelson in Sweden. Since then, SRS-A attracted attention because of its relationship with asthmatic attack which continues for a long period of time.

Further, it was proved that the liberation of leukotrienes occurred in the skin reaction and the reaction of the nasal mucosa as well, that the inhalation of leukotrienes brought about asthmatic attack, and that the concentration of leukotrienes was significantly increased in the blood or bronchoalveolar cleaning fluid (BACF) of patients suffering from asthmatic attack. From these facts, it is believed that there is a high possibility for leukotrienes to be a key mediator of the asthmatic attack.

Hitherto, antiasthmatic agents have been developed based on a general idea that the liberation of the chemical mediator should be inhibited. Representative examples of such an antiasthmatic agent include Intal which has been put on the market since 1969. However, in the conventional antiasthmatic agents including Intal, the mediator liberation inhibitory concentration in vitro is different from that in vivo. Further, there is much unknown matter about the action mechanism, and few physicians are satisfied with the clinical effect of the conventional antiasthmatic agents. Therefore, the development of an antiasthmatic agent exhibiting an excellent clinical effect has been strongly desired.

US-A-4581457 discloses compounds having the formula:

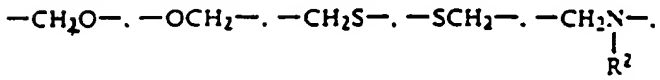


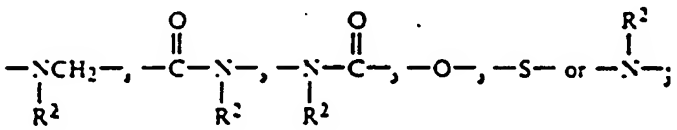
wherein

X is -N-;

W is -O- or -S-;

Y is





n is 0-8;

R^1 is hydrogen, loweralkyl, loweralkoxy, lower alkanoyl, halo, trifluoromethyl, cyano or nitro;

R^2 is hydrogen or loweralkyl;

or a pharmaceutically acceptable salt thereof.

These compounds are noted to be useful for treating leukotriene-mediated naso-bronchial obstructive air-

passageway conditions such as allergic bronchial asthma.

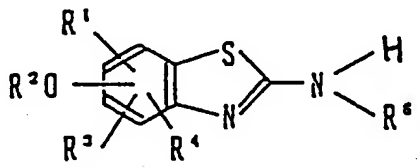
Under these circumstances, the present inventors have made extensive and intensive studies for a long period of time with a view to developing a novel therapeutic agent for asthma which exhibits an excellent effect in clinical test as well with respect to the leukotriene production inhibitory action due to 5-lipoxygenase inhibition.

As a result, the present inventors have found that the object can be attained by the following benzothiazole derivative, which has led to the completion of the present invention.

Therefore, an object of the present invention is to provide a novel benzothiazole derivative and a pharmacologically acceptable salt thereof useful as an antiasthmatic agent. Another object of the present invention is to provide a process for preparing said compound or a pharmacologically acceptable salt thereof. A further object of the present invention is to provide a pharmaceutical comprising as an effective ingredient said compound or pharmacologically acceptable salt thereof.

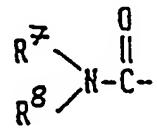
(Summary of the Invention)

The object compound of the present invention is a benzothiazole derivative and a pharmacologically acceptable salt thereof represented by the following general formula (I):

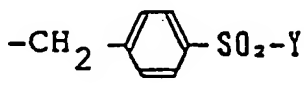


wherein R^1, R^3, and R^4 which may be the same or different are each a hydrogen atom, a straight-chain or branched alkyl group having 1 to 6 carbon atoms, a halogen atom, a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, an aroyl group selected from benzoyl, toluoyl and naphthoyl, a heteroaroyl group selected from furoyl, nicotinoyl and isonicotinoyl, a hydroxyl group, a straight-chain or branched alkoxy group having 1 to 6 carbon atoms, a hydroxy straight-chain or branched alkyl group having 1 to 6 carbon atoms, a nitro group, an amino group, or a dialkylamino group in which the alkyl groups are straight-chain or branched and have 1 to 6 carbon atoms, provided that any two of R^1, R^3 and R^4 may be combined together to form an aromatic ring which may consist of only carbon atoms or additionally contain a nitrogen atom,

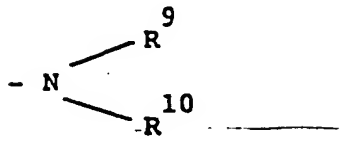
R^2 is a hydrogen atom, a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, an aroyl group selected from benzoyl, toluoyl and naphthoyl, a heteroaroyl group selected from furoyl, nicotinoyl and isonicotinoyl, or a group represented by the formula



wherein R^7 and R^8 which may be the same or different are each a hydrogen atom or a straight-chain or branched alkyl group having 1 to 6 carbon atoms, and R^5 is a group represented by the formula:



wherein Y is a straight-chain or branched alkyl group having 1 to 6 carbon atoms or a group represented by the formula



wherein R^9 and R^{10} which may be the same or different are each a hydrogen atom, a straight-chain or branched alkyl group having 1 to 6 carbon atoms, a straight-chain or branched alkoxy group having 1 to 6 carbon atoms or a hydroxy straight-chain or branched alkyl group having 1 to 6 carbon atoms.

It is preferable in the definition of the benzothiazole of the invention that the benzothiazole ring has R^2O- at 6-position.

The preferable compounds include:

6-hydroxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethyl-benzothiazole,

6-hydroxy-2-(4-sulfamoylbenzylamino)-5,7-dibromobenzothiazole and

4-hydroxy-2-(4-sulfamoylbenzylamino)-5,7-dibromobenzothiazole.

The invention also provides a pharmaceutical composition which comprises a therapeutically effective amount of the benzothiazole compound as defined above or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier, a therapeutic composition for the leukotriene production-inhibitory action due to 5-lipoxygenase inhibition, which comprises a therapeutically effective amount of the benzothiazole compouond as defined above or a pharmacologically acceptable salt thereof and a pharmcologically acceptable carrier and an anti-allergic agent which comprises the benzothiazole compound as defined above or a pharmacologically acceptable salt thereof.

The invention, in addition, provides a method for treating a desease of a human patient, caused by production of the leukotriene, by administering thereto a therapeutically effective amount of a benzothiazole compound as defined above or a pharmacologically acceptable salt thereof.

With respect to the compound (I) of the present invention, the term "alkyl group" used in the above definition of R^1, R^3, R^4, R^7, R^8 and R^5 is intended to mean a straight-chain or branched alkyl group having 1 to 6 carbon atoms, and examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl (amyl), isopenthyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, and 1-ethyl-2-methylpropyl groups. Among them, methyl, ethyl, propyl, isopropyl groups etc. are preferable.

The term "alkoxy group" used in the above definition of R^1, R^3, R^4 and R^5 is intended to mean a straight-chain or branched alkoxy group having 1 to 6 carbon atoms, and examples thereof include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tertbutoxy, pentyloxy, isopentyloxy, neopentyloxy, tertpentyloxy, 1-methylbutoxy, 2-methylbutoxy, 1,2-dimethylpropoxy, and hexyloxy groups. Among them, methoxy, ethoxy groups etc. are preferable.

The term "hydroxy alkyl group" used in the above definition of R^1, R^3, R^4 and R^6 is intended to mean a group comprising the above-defined alkyl group having 1 to 6 carbon atoms and a hydroxyl group bonded to any of the carbon atoms of the alkyl group, and preferable examples thereof include hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, and 3-hydroxypropyl groups.

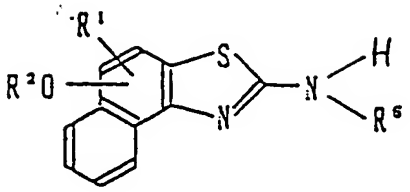
The term "halogen atom" used in the definition of R^1, R^3 and R^4 is intended to mean chlorine, bromine, iodine, and fluorine. Among them, chlorine and bromine are preferable.

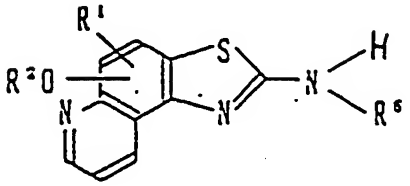
The term "alkanoyl group" used in the definition of R^1, R^2, R^3, and R^4 is intended to include lower alkanoyl groups such as formyl, acetyl, propionyl, butyryl, valeryl, isovaleryl, and pivaloyl groups.

The term "dialkylamino group" used in the definition of R^1, R^3 and R^4 is intended to mean a dialkylamino group derived from the above-defined alkyl group. Most preferable examples of the dialkylamino group include a dimethylamino group.

In the definition of R^1, R^3, and R^4, the expression "any two of R^1, R^3, and R^4 may be combined together to form an aromatic ring which may consist of only carbon atoms or additionally contain a nitrogen atom" is intended to mean, for example, the formation of a benzene ring, a pyridine ring, or a pyrimidine ring by combination of carbon atoms adjacent to each other and located at the fourth to seventh positions of the phenyl ring in the benzothiazole ring.

Preferable examples thereof include:

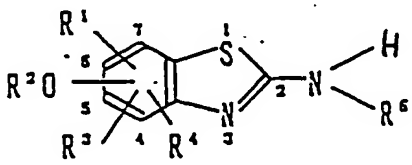




wherein R^1, R^2, R^5, and R^6 are as defined above.

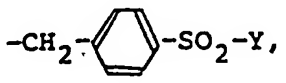
The term "pharmaceutically acceptable salt" include salts of inorganic acids, such as hydrochloride, hydrobromide, sulfate, and phosphate; those of organic acids, such as acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, and toluenesulfonate; and those of amino acids such as arginine, aspartic acid, and glutamic acid. Further, certain compounds of the present invention are in the form of metallic salts such as Na, K, Ca, and Mg salts, and these metallic salts are also within the scope of the pharmacologically acceptable salt. Furthermore, some compounds of the present invention may be in the form of a hydrate. The compounds according to the present invention may have asymmetric carbon atoms when they have particular substituents so that they may be present in the form of stereoisomers. These are, of course, within the scope of the present invention.

The compound (I) of the present invention has the following structure having a benzothiazole skeleton:

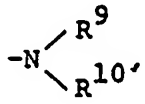


(I)

wherein R^1, R^2, R^3, R^4, and R^6 are as defined above. Specifically, the compound (I) of the present invention has a benzothiazole skeleton, and the 2-position thereof is substituted. Further, it is possible for the phenyl ring constituting the benzothiazole skeleton to have up to 4 substituents. It is noted in this connection that the group represented by the formula $-OR^2$ is most preferably attached to the 6-position and R^2 is most preferably H. R^6 is a group represented by the formula



wherein Y is as defined above. Y is preferably a group represented by the formula



wherein R^9 and R^{10} are as defined above.

Therefore, the characteristic features of the structure of the compound according to the present invention reside in that the phenyl ring of the benzothiazole skeleton has a group represented by the formula $-OR^2$ as one of the substituents and that the 2-position of the benzothiazole skeleton is substituted with various amino groups.

The compound of the present invention is valuable as various pharmaceuticals based on the leukotriene liberation inhibitory action, particularly as an antiallergic agent and a therapeutic and preventive agent for asthma and has a novel skeleton which has not been found in the conventional compounds exhibiting this kind of drug effect.

Process

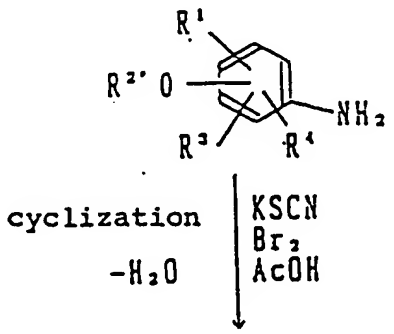
The compound of the present invention may be prepared by various processes. Representative processes for preparing the compound of the present invention will now be described.

In the general formula (I), when R^2 is H, i.e., when any of the 4-, 5-, 6-, and 7-positions are a hydroxyl group, it is preferred that the object substance be prepared by conducting a reaction with the hydroxyl group protected in the form of a methyl ether and conducting demethylation in the final step in which each object substance is obtained (e.g., according to the method of Process 8 which will be described later).

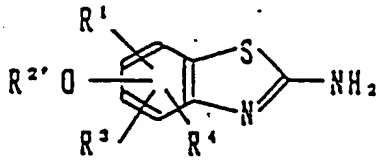
In the following Processes 1, 5, 6, and 7, $R^{2'}$ includes a methyl group in addition to the groups defined with respect to R^2. When $R^{2'}$ is a methyl group, the compound is not an object compound but a compound which can be used as a starting material in any of the processes.

Process 1

In the general formula (I), if R^6 were to represent a hydrogen atom, the compound could be prepared, e.g., by the following process:



(II)



(III)

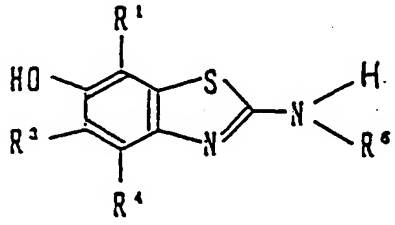
Specifically, a compound represented by the general formula (II) is cyclized according to an ordinary method to-prepare a compound represented by the general formula (III).

In this reaction, the compound (II) having an amino group is cyclised by making use of potassium thiocyanate and bromine. For example, this reaction is conducted according to the method described in Beilstein, 27(2), p.334. Examples of a reaction solvent include an acetic acid-water solvent system in which the ratio of acetic acid to water is 1 : 1 to 95 : 5.

The reaction temperature usually ranges from 0 °C to room temperature.

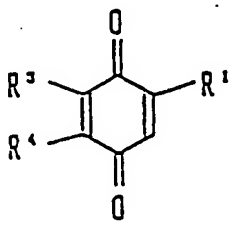
Process 2

When the object compound represented by the general formula (I) is a compound represented by the following formula:



(IV)

such a compound can be prepared also by the following cyclization:



(V)

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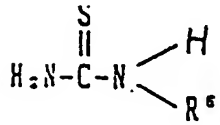

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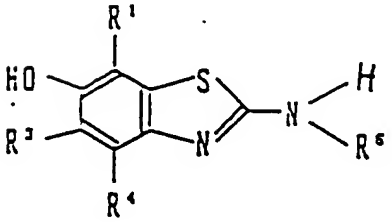


(IV)

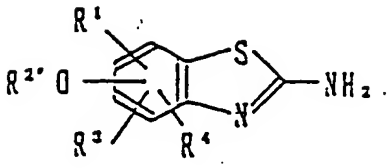
wherein R^1, R^3, R^4, and R^6 are as defined above.

In this process, a compound (IV) is prepared by allowing 1,4-benzoquinone (V) to condense with thiourea (VI) in the presence of concentrated hydrochloric acid according to the method described in J. Org. Chem., 35, 4103 (1970).

Methanol, ethanol or the like is used as the solvent, and the reaction temperature ranges from 0 °C to a temperature at which the solvent is refluxed.

Process 5 (production via Schiff base)

The compound of the present invention can be prepared also by the following process:



(XII)

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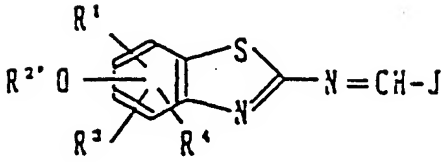
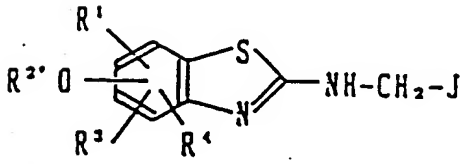
J-CHO (XV)



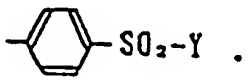
(XVI)

reduction



(XVII)

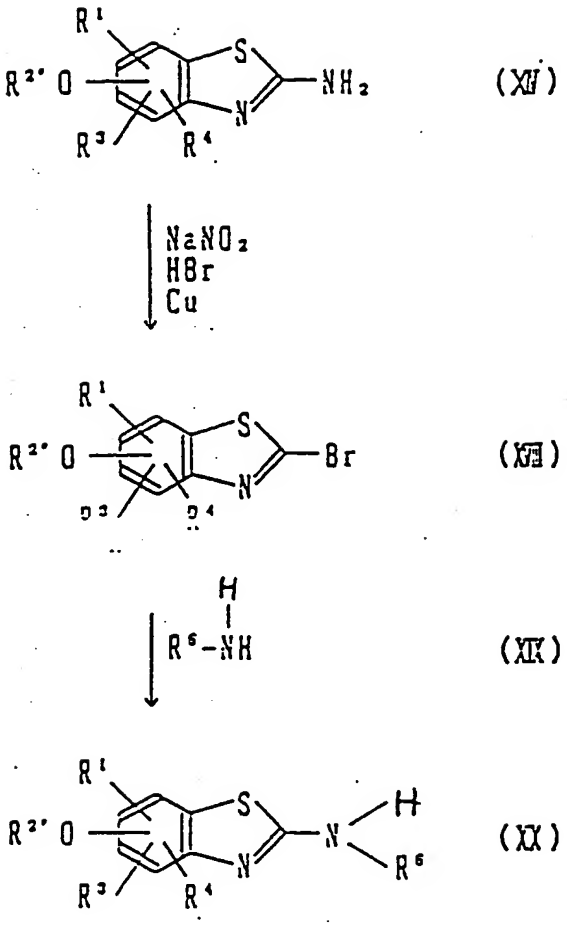
wherein R^1, $R^{2'}$, R^3 and R^4 are as defined above, and J represents



In this process, a compound (XIV) having an amino group is reacted with an aldehyde (XV) while removing formed water, thereby preparing a Schiff base. In this case, any solvent which does not take part in the reaction can be used as the solvent. Preferable examples of the solvent include benzene and toluene. The reaction temperature ranges from room temperature to a temperature at which the solvent is refluxed. The addition of a small amount of ammonium acetate brings about a rapid progress of the reaction.

Then, the schiff base (XVI) thus obtained is reduced to an amine compound (XVII). Examples of the reducing agent used include lithium aluminum hydride, sodium borohydride, and sodium cyanoborohydride. Further, it is possible to conduct catalytic reduction in the presence of a catalyst comprising palladium-carbon, platinum oxide, Raney nickel, or the like. Any solvent which does not take part in the reaction may be used as the solvent for the reaction. The reaction temperature ranges from 0°C to a temperature at which the solvent is refluxed. Preferable examples of the solvent for the reaction include tetrahydrofuran and diethyl ether when aluminum hydride is used; methanol, ethanol, and a mixed solvent comprising water and alcohol when sodium borohydride or cyanoborohydride is used; and ethyl acetate, methanol, and ethanol in the case of the catalytic reduction.

Process 6 (production via isobromide)



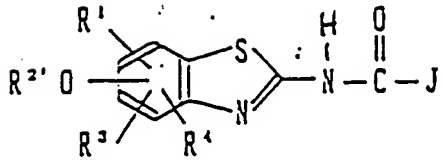
wherein R^1, $R^{2'}$, R^3, R^4, and R^6 are as defined above.

A compound (XIV) having an amino group is diazotised according to the method described in Organic Synthesis, Collective Volume I, p.135 and decomposing the formed diazonium salt to prepare an iminobromo compound (XVIII). Example of the diazotizing agent include sodium nitrite and hydrobromic acid. Further, hydrobromic acid and copper are used in the decomposition of the diazonium salt. Any solvent which does not take part in the reaction can be used as the solvent, and hydrobromic acid is also used as the solvent. The reaction temperature ranges from 0 °C to a temperature at which the solvent is refluxed.

The iminobromo compound (XVIII) is reacted with an amine in the presence of a base to prepare a compound (XX). Any base may be used as the base, and any solvent which does not take part in the reaction may be used as the solvent. Further, the reaction may be conducted in the absence of any solvent. The reaction temperature ranges from room temperature to 180 °C.

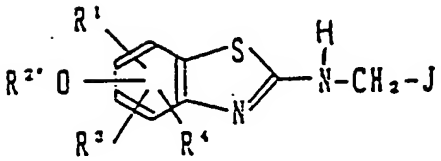
Process 7 (reduction of amide compound to amine compound)

When R^6 in the general formula (I) is a group represented by the formula $-CH_2-J$, wherein J is as defined above, the compound of the present invention can be prepared also by the following process:



(XIII)

reduction

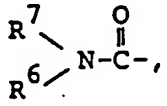


(XII)

wherein R^1, $R^{2'}$, R^3, R^4, and J are as defined above.

The amide (XIII) is reduced into an amine compound (XXI). Lithium aluminum hydride and diborane are used as the reducing agent. Any solvent which does not take part in the reaction may be used as the solvent for the reaction. Preferable examples of the solvent include tetrahydrofuran and diethyl ether. The reaction temperature ranges from room temperature to a temperature at which the solvent is refluxed.

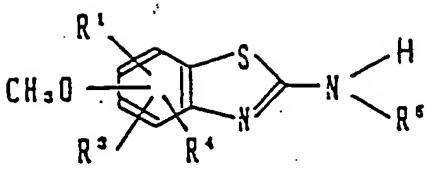
When $R^{2'}$ is an acyl group or a group represented by the formula



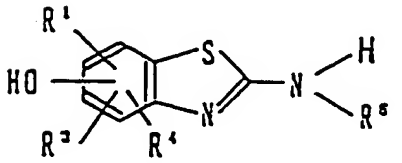
wherein R^7 and R^8 are as defined above, diborane is used, while when $R^{2'}$ is any other group, lithium aluminum hydride is used.

Process 8 (demethylation)

When R^2 in the general formula (I) is H, the compound of the present invention can be prepared also by the following process:



(XXII)



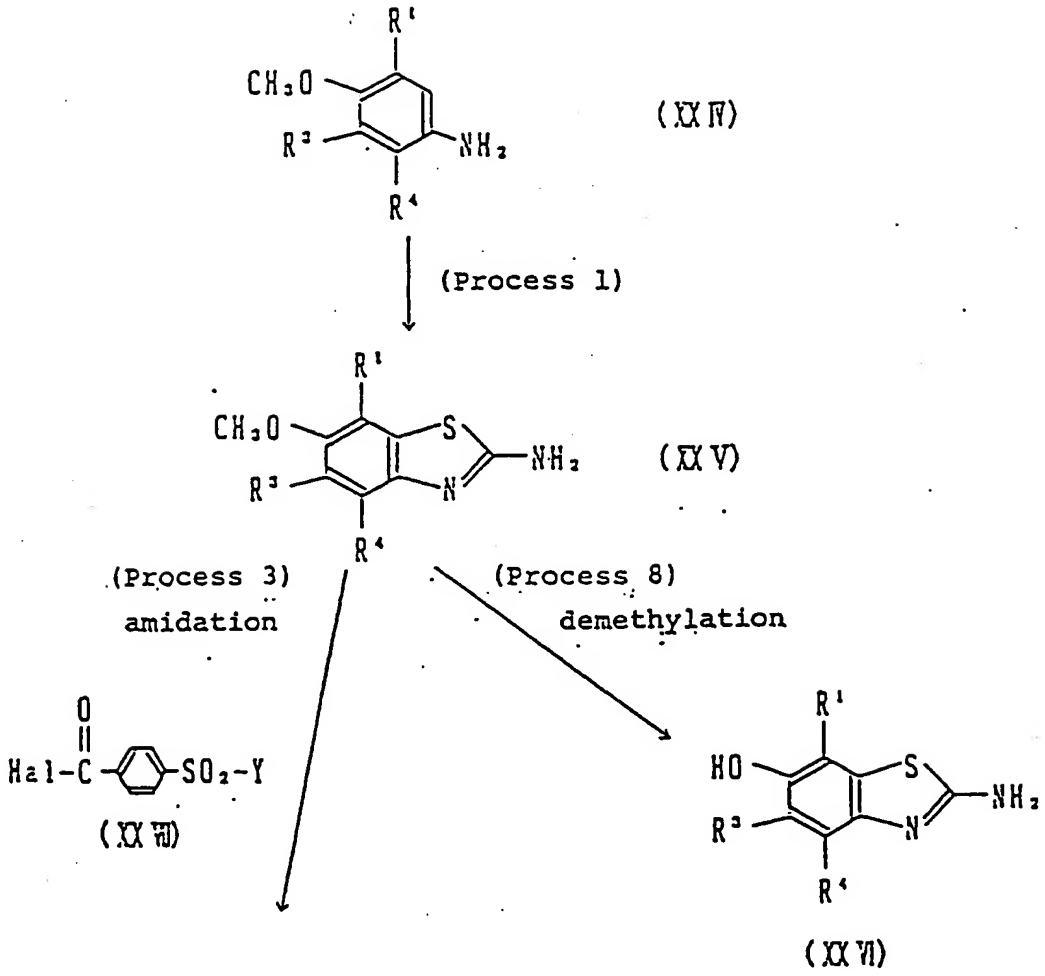
(XXIII)

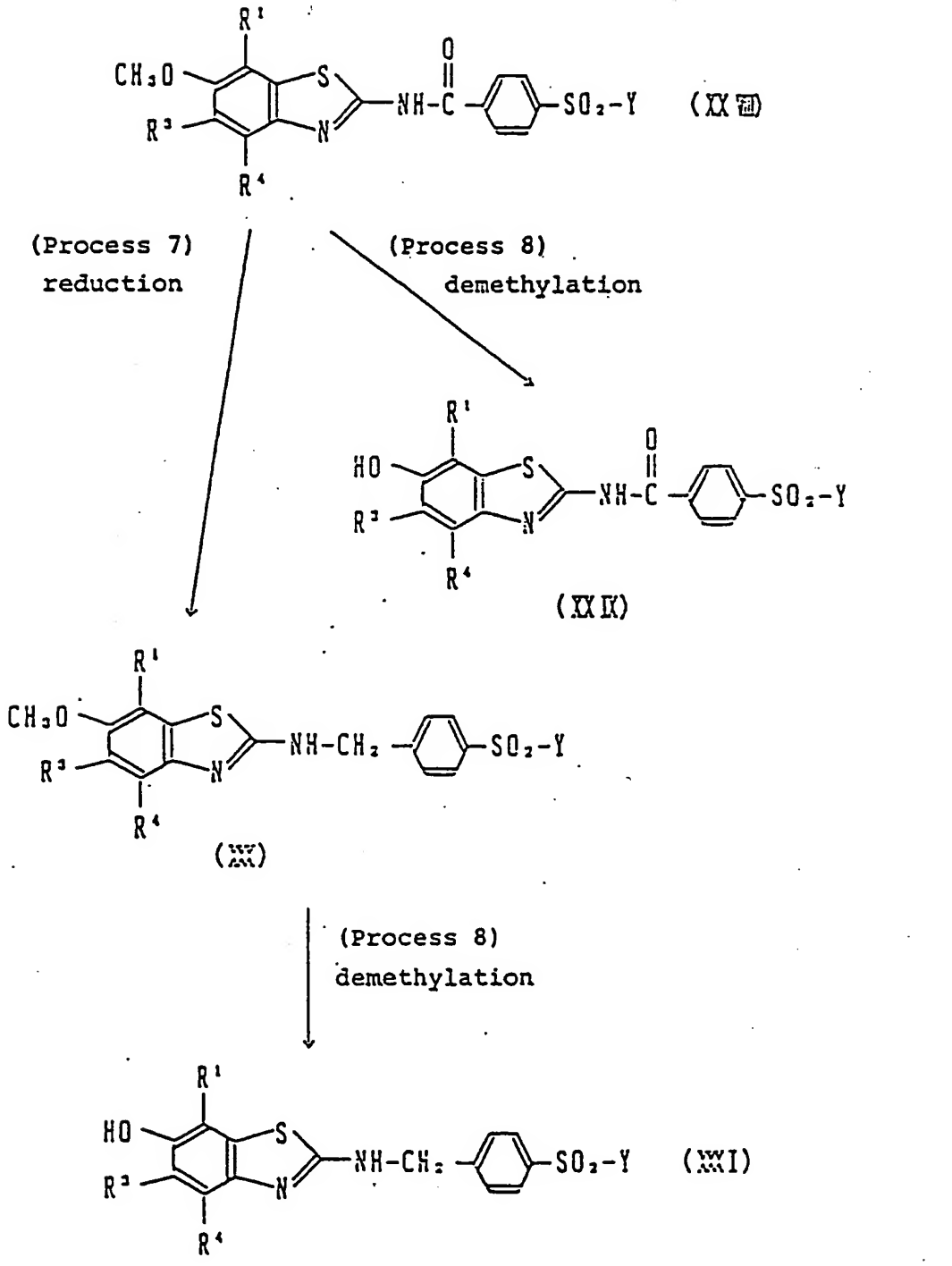
wherein R^1, R^3, R^4, and R^6 are as defined above.

A methyl compound (XXII) is demethylated into a demethylated compound (XXIII). Examples of the demethylating agent used include boron tribromide, trimethylsilyl iodide, and hydrogen bromide/acetic acid. Any solvent which does not take part in the reaction can be used as the solvent. Methylene chloride, chloroform, etc. are particularly preferable. The reaction temperature ranges from 0°C to a temperature at which the solvent is refluxed.

As described above, when R^2 is H, the reaction is usually conducted by making use of a starting material comprising a compound in which the hydroxyl group is protected in the form of a methyl ether, and the demethylation is conducted in the final step of preparing each object compound, thereby obtaining each object compound.

For easy understanding, a specific example will now be given.


(XXIV)
(Process 1)
(XXV)
(Process 3)
amidation
(Process 8)
demethylation
(XXVII)
(XXVI)



wherein R^1, R^3, R^4, and Y are as defined above and Hal is a halogen atom.

The effect of the present invention will now be described in more detail with reference to the following examples of pharmacological experiment.

Examples of pharmacological experiment

Effect on generation of leukotriene C_4 (LT) from sliced lung of guinea pig

Experimental method

An antiovalbumin guinea pig serum (1/10 dilution; 0.5 mℓ/100 g) was intravenously injected into a male Hartley guinea pig (300-350 g) for passive sensitization. 16 to 18 hr after the passive sensitization, the blood was removed by circulation of the Tyrode solution and the lung was extirpated. The extirpated lung was cut into small pieces having a size of 1 mm x 1 mm x 1 mm while cooling the lung with ice. The pieces were washed, and 150 mg of the pieces was suspended on 1.8 mℓ of the Tyrode solution, followed by incubation at 37°C for 5 min. A 3 μm test compound (the compound of the present invention) solution was added thereto, followed by incubation for 10 min. An antigen solution (ovalbumin; a final concentration of 10 μm/mℓ) was added thereto, followed by incubation for additional 15 min. The mixture was filtered through a nylon mesh. 100 μℓ of the filtrate was subjected to determination of the amount of leukotriene C_4 (LTC_4) with an RzA kit.

Experimental results

The percentage leukotriene C_4 (LTC_4) liberation inhibition of each compound (indicated by compound No. used in the Examples which will be described later) is shown in Table 1.

The compound No. in Table 1 corresponds to the compound No. in the Examples.

Table 1

Compound No.	Percentage inhibition 3 μM (%)
30	79
31	62
32	44
33	46
34	70
37	39
86	31
87	32

From the above results of the pharmacological experiment, it is apparent that the compound of the present invention inhibits the production of leukotriene. Therefore, the compound of the present invention is useful as a pharmaceutical based on the leukotriene production inhibitory action. The compound of the present invention is effective against allergy, especially asthma, and other diseases which are considered to be caused by leukotrines, e.g., affections of the skin, such as psoriasis and eczema, allergic rhinitis, and affection of a cardiovascular system.

Further, various experiments conducted by the present inventors have revealed that the compound of the present invention can suppress the production of leukotriene due to 5-lipoxygenase inhibition and further exhibits its effect in oral administration in the case of an asthma model. Therefore, the compound of the present invention is particularly useful as a therapeutic and preventive agent and therefore invaluable.

Further, the compound of the present invention has a low toxicity and a high safety and is therefore useful also from these viewpoints.

Specifically, with respect to the safety, all of the compounds of the present invention exhibited no serious toxicity in a single oral administration (300 mg/kg) to a guinea pig (Hartley; a weight of 300 - 350 g).

Therefore, the compound of the present invention is useful as a therapeutic composition for inhibiting the leukotriene production due to 5-lipoxygenase inhibition.

Specifically, the compound of the present invention is useful as therapeutic and preventive agents for diseases which are considered to be caused by leukotrienes, e.g., affection of the skin, such as psoriasis and eczema, and allergic diseases such as allergic rhinitis and asthma. The compound of the present invention is particularly useful as an antiasthmatic agent.

The compound of the present invention is administered as a therapeutic and preventive agent for these diseases in the form of tablets, powders, granules, capsules, medicated syrups, or inhalations. The dose of the compound of the present invention will remarkably vary depending upon the symptom, age, kind of the diseases, etc. In general, the compound may be administered in a dose of about 0.1 to 1000 mg, preferably 1 to 500 mg per adult per day in one to several portions.

Pharmaceutical preparations are prepared from the compound of the present invention by making use of a commonly accepted carrier for pharmaceutical preparations according to an ordinary method.

Specifically, when a solid preparation for oral administration is prepared, the effective ingredient is blended with a vehicle and, if necessary, a binder, a disintegrator, a lubricant, a colorant, a corrigent, etc., followed by preparation of tablets, coated tablets, granules, powders, and capsules.

Examples of the vehicle include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose, and silicon dioxide. Examples of the binder include polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylmethylcellulose, calcium citrate, dextrin, and pectin. Examples of the lubricant include magnesium stearate, talc, polyethylene glycol, silica, and hydrogenated vegetable oil. Any colorant of which the addition to pharmaceuticals is officially allowed can be used as the colorant. Examples of the corrigent include cacao powder, menthol, aromatic powder, mentha powder, borneol, and powdered cinnamon bark. It is a matter of course that a sugar coating, a gelatin coating and, if necessary, suitable other coatings may be applied on these tablets and granules.

When parenteral preparations are prepared, a pH modifier, a buffering agent, a stabilizer, a solubilizing agent, etc. are added to the effective ingredient, followed by preparation of parenteral preparations for subcutaneous injection, intramuscular injection, and intravenous injection according to an ordinary method.

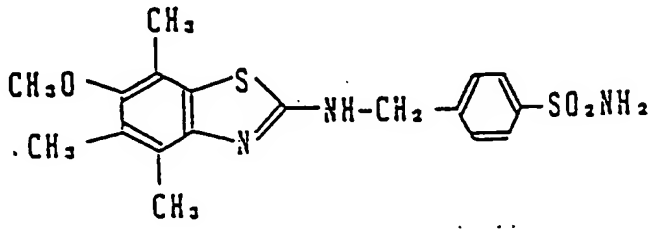
Examples of the present invention will now be described. It is needless to say that the invention of the present invention is not limited to these only.

Although the following Examples also include starting materials, the object compounds have each a compound No. attached thereto.

Further, in the column of ^{1}H-NMR of Tables 2 to 12, the signals of active hydrogen which can be replaced with D_2O were omitted.

Preparative Example 6

6-Methoxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethylbenzothiazole

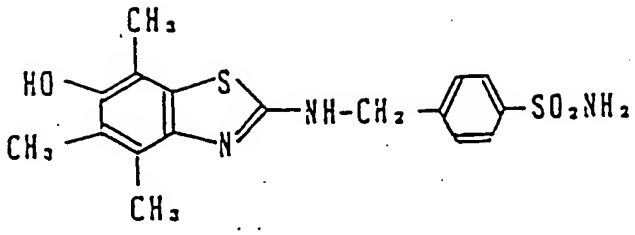


38.7 g of lithium aluminum hydride was suspended in 1.2 ℓ of tetrahydrofuran. 41.4 of 6-methoxy-2-(4-sulfamoylbenzamido)-4,5,7-trimethylbenzothiazole was added at room temperature to the suspension while stirring. The mixture was heated under reflux for 40 min, and the reaction mixture was cooled with ice, followed by addition of water. The formed white precipitate was dissolved by addition of concentrated hydrochloric acid. An aqueous saturated sodium bicarbonate solution was added thereto to adjust the pH value to 4 to 5, followed by extraction with ethyl acetate. The organic phase was washed with water and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was recrystallized from acetone/methanol, thereby preparing 20.7 g of the title compound.

- ^{1}H-NMR (DMSO-d_6) δ : 2.14(3H,s), 2.22(3H, s), 2.34(3H, s), 3.56(3H, s), 4.58(2H, d, J=7), 7.23(2H, br, s), 7.47(2H, d, J=10), 7.72(2H, d, J=10), 8.32(1H, br, t, J=7)

Example 7

6-Hydroxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethylbenzothiazole

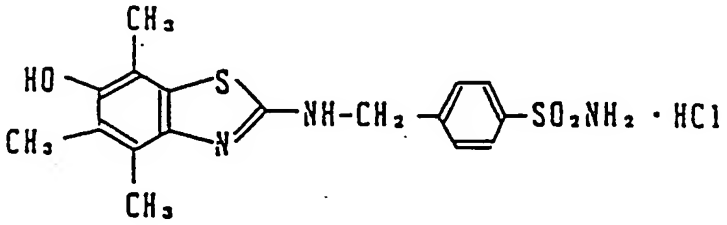


20.7 g of 6-methoxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethylbenzothiazole was suspended in 500 mℓ of methylene chloride. 200 mℓ of a methylene chloride solution of boron tribromide (1M) was added to the suspension while stirring at room temperature, followed by heating under reflux for 30 min. The reaction mixture was allowed to cool, poured into an aqueous saturated sodium bicarbonate solution for neutralization and then extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resulting crystal was separated by filtration, thereby preparing 19.5 g of the title compound.

- ^{1}H-NMR (DMSO-d_6) δ : 2.13(3H, s), 2.20(3H, s), 2.35(3H, s), 4.57(2H, d, J=7Hz), 7.24(2H, br, s), 7.50-(2H, d, J=9Hz), 7.74(2H, d, J=9Hz), 8.84(1H, br, s), 8.14(1H, br, t, J=7Hz)

Example 8

6-Hydroxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethylbenzothiazole hydrochloride



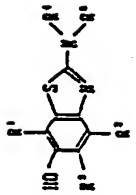
19.5 g of 6-hydroxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethylbenzothiazole was dissolved in 2 ℓ of ethanol by heating. Ethanol containing hydrogen chloride dissolved therein was added thereto, followed by cooling. The formed crystal was separated by filtration, thereby preparing 19.5 g of the title compound in the form of a white crystal.

- m.p. (°C): 210 (dec.)
- ^{1}H-NMR (DMSO-d_6) δ : 2.15(3H, s), 2.20(3H, s), 2.38(3H. s), 4.84(2H, br, s), 7.56(2H, d, J=9Hz), 7.78-(2H, d, J=9Hz)

Example 9

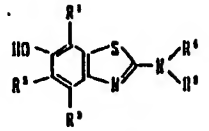
The procedures described in Preparative Example 6 and Example 7 were successively conducted to prepare compounds shown in Table 4.

Table 4



Compd. No.	R^1	R^2	R^3	R^4	R^5	Salt	m.p. (°C)	^1H-NMR
30	CH_3-	CH_3-	CH_3-	H		free	204 ~ 205	(DMSO-d_6) δ : 2.10 (3H, s), 2.16 (3H, s), 2.33 (3H, s), 2.16 (3H, s), 4.59 (2H, d, J=6Hz), 7.60 (2H, d, J=9Hz), 7.86 (2H, d, J=9Hz)

Table 4 (cont'd)



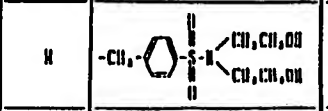
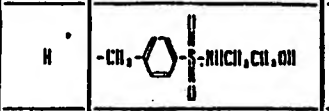
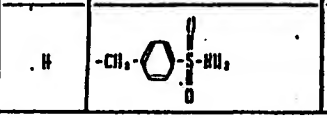
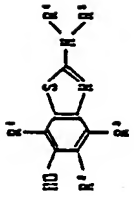
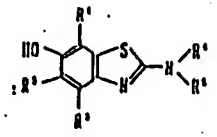
Compd. No.	R^1	R^2	R^3	R^4	R^5	Salt	m.p. (°C)	^{1}H-NMR
31	CH_3-	CH_3-	CH_3-	H		hydrochloride	222 ∼ 225	(DMSO-d_6) δ : 2.14 (3H, s), 2.20 (3H, s), 2.36 (3H, s), 3.13 (2H, t, J=6Hz), 3.48 (4H, t, J=6Hz), 4.80 (2H, s), 7.56 (2H, d, J=9Hz), 7.71 (2H, d, J=9Hz)
32	CH_3-	CH_3-	CH_3-	H		free	203 ∼ 206	($CDCl_3$) δ : 1.09 (6H, t, J=8Hz), 2.19 (3H, s), 2.25 (3H, s), 2.40 (3H, s), 3.17 (4H, q, J=8Hz), 7.56 (2H, s), 7.36 (2H, d, J=9Hz), 7.64 (2H, d, J=9Hz)
33	CH_3-	CH_3-	CH_3-	H		free	105 ∼ 107	(DMSO-d_6) δ : 2.14 (3H, s), 2.18 (3H, s), 2.36 (3H, s), 2.78 (2H, t, J=7Hz), 3.33 (2H, t, J=7Hz), 4.56 (2H, d, J=6Hz), 7.50 (2H, d, J=9Hz), 7.68 (2H, d, J=9Hz)
34	CH_3-	CH_3-	CH_3-	H		hydrochloride	210 (dec.)	(DMSO-d_6) δ : 2.15 (3H, s), 2.20 (3H, s), 2.38 (3H, s), 4.84 (2H, s), 7.56 (2H, d, J=9Hz), 7.78 (2H, d, J=9Hz)

Table 4 (cont'd)



Compd. No.	R^1	R^2	R^3	R^4	R^5	Salt	m.p. (°C)	^{1}H-NMR
37			H	H		hydrochloride	170 ~ 172	(DMSO-d$_6$) δ : 1.16 (6H, d, J=6Hz), 1.28 (6H, d, J=6Hz), 3.20~3.70 (2H, m), 4.30 (2H, s), 7.23 (1H, s), 7.61 (2H, d, J=10Hz), 7.84 (2H, d, J=10Hz)
38			H	H		free	101 ~ 102	(DMSO-d$_6$) δ : 1.12 (6H, d, J=6Hz), 1.26 (6H, d, J=6Hz), 2.30~2.60 (6H, m), 3.10 (4H, t, J=6Hz), 3.30~3.60 (6H, m), 4.58 (2H, d, J=6Hz), 6.98 (1H, s), 7.18 (2H, d, J=10Hz), 7.70 (2H, d, J=10Hz)
39			H	H		free	110 ~ 112	(DMSO-d$_6$) δ : 1.14 (6H, d, J=7Hz), 1.26 (6H, d, J=7Hz), 2.95~3.84 (2H, m), 4.18 (2H, s), 4.64 (2H, d, J=6Hz), 7.00 (1H, s), 7.38 (2H, d, J=10Hz), 7.88 (2H, d, J=10Hz)

Table 4 (cont'd)



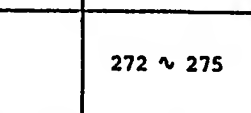
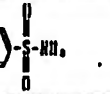
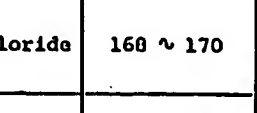
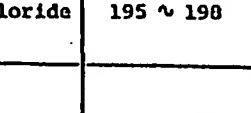
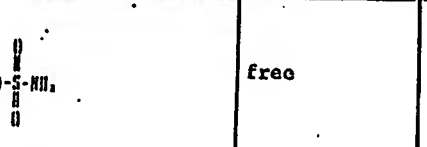
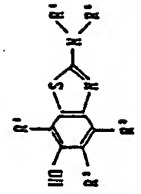
Compd. No.	R^1	R^2	R^3	R^4	R^5	Salt	m.p. (°C)	^{1}H-NMR
41	H	H	H	H		free	272 ∿ 275	(DMSO-d_6) δ : 4.76(2H, s), 6.70(1H, dd, J=10Hz, 3Hz), 7.06 (1H, d, J=3Hz), 7.20(1H, d, J=10Hz), 7.54(2H, d, J=10Hz), 7.8(2H, d, J=10Hz)
42		CH_3-	CH_3-	H		hydrochloride	160 ∿ 170	(DMSO-d_6) δ : 1.24(6H, d, J=7Hz), 2.13(3H, s), 2.36(3H, s), 3.50(1H, m), 4.76(2H, s), 7.50(2H, d, J=10Hz), 7.74(2H, d, J=10Hz)
43	CH_3-	CH_3-	H	H		hydrochloride	195 ∿ 198	(DMSO-d_6) δ : 2.24(6H, s), 4.00(2H, s), 7.19(1H, s), 7.60 (2H, d, J=10Hz), 7.80(2H, d, J=10Hz)
45						free	232 ∿ 234 (dec.)	(DMSO-d_6) δ : 1.34(6H, d, J=8Hz), 3.5 ∼3.7(1H, m), 4.65 (2H, d, J=6Hz), 7.2 ∼7.4(2H, m), 7.54(2H, d, J=10Hz), 7.75(2H, d, J=10Hz), 8.0 ∼8.3(2H, m)

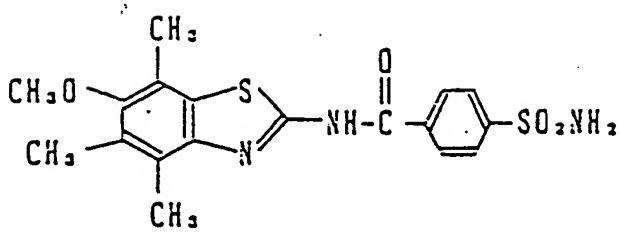
Table 4 (cont'd)



Compd. No.	R^1	R^2	R^3	R^4	R^5	Salt	m.p. (°C)	^1H-NMR
46		CH_3-	CH_3-	H		free	156 ~ 157	(DMSO-d_6) δ ; 1.28 (3H, d, J=6Hz), 2.14 (3H, s), 2.38 (3H, s), 4.58 (2H, d, J=6Hz), 5.68 (1H, m), 7.46 (2H, d, J=10Hz), 7.76 (2H, d, J=10Hz)
47		CH_3-	CH_3-	H		free	228 ~ 230	(DMSO-d_6) δ ; 2.22 (3H, s), 2.50 (3H, s), 2.72 (3H, s), 4.68 (2H, d, J=6Hz), 7.63 (2H, d, J=10Hz), 7.85 (2H, d, J=10Hz)
48						free	229 ~ 230	(DMSO-d_6) δ ; 1.94 (6H, s), 2.02 (3H, s), 4.49 (2H, d, J=7Hz), 7.32 (2H, d, J=10Hz), 7.56 (2H, d, J=10Hz)
49	CH_3-		H	H	-SO_2NH_2	hydrochloride	210 ~ 220	(DMSO-d_6) δ ; 1.22 (3H, s), 1.32 (3H, s), 4.58 (2H, s), 7.6 ~ 7.9 (4H, m)

Comparative Preparative Example 1

6-Methoxy-2-(4-sulfamoylbenzamido)-4,5,7-trimethylbenzothiazole

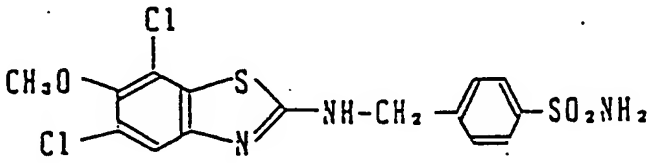


68 g of 4-sulfamoylbenzoic acid was suspended in 500 mℓ of dimethoxyethane. 50 mℓ of thionyl chloride was added to the suspension, followed by heating under reflux for 5 hr. Dimethoxyethane, thionyl chloride, and hydrogen chloride were distilled off in vacuo. The residue was dissolved in 500 mℓ of tetrahydrofuran. 50 g of 2-amino-6-methoxy-4,5,7-trimethylbenzothiazole (synthesized from 1-amino-4-methoxy-2,3,5-trimethylbenzene in the same manner as that described in Example 1) and 100 mℓ of pyridine were added to the resulting solution while cooling the solution with ice, followed by stirring at room temperature for 1 hr. The reaction mixture was poured into ice/water and then extracted with ethyl acetate under acidic conditions in the presence of hydrochloric acid. The organic phase was washed with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was then recrystallized from methanol, thereby preparing 41.4 g of the title compound.

^{1}H-NMR (DMSO-d_6) δ : 2.24(3H, s), 2.38(3H, s), 2.52(3H, s), 3.63(3H, s), 7.49(2H, br, s), 7.89(2H, d, J = 10H_z), 8.20(2H, d, J = 10H_z), 12.83(1H, br, s).

Preparative Example 21

5,7-Dichloro-6-methoxy-2-(4-sulfamoylbenzylamino) benzothiazole



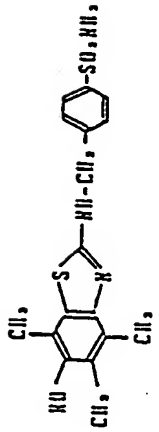
2.0 g of 5,7-dichloro-6-methoxy-2-(4-sulfamoylbenzamido)benzothiazole prepared in the same manner as that of Comparative Preparative Example 1 was dissolved in 50 mℓ of tetrahydrofuran. 15 mℓ of a tetrahydrofuran solution of diborane (1M) was added at room temperature to the resulting solution, followed by heating under reflux for 1 hr. The reaction mixture was allowed to cool. An aqueous ammonium chloride solution was added thereto, followed by extraction with ethyl acetate. The organic phase was washed with water and dried over anhydrous magnesium sulfate. Then the solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography, thereby preparing 0.7 g of the title compound.

- ^{1}H-NMR (DMSO-d_6) δ : 3.82(3H, s), 4.67(2H, d, J = SH_z), 7.48(1H, s), 7.52(2H, d, J = 10H_z), 7.82(2H, d, J = 10Hz)

Example 22

Compounds shown in Table 8 were prepared in the same manner as that of Preparative Example 21.

Table 8

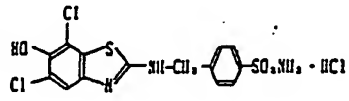
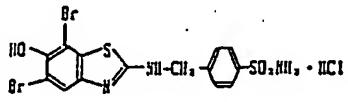
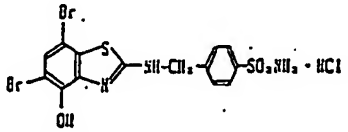


Compd. No.	R	Salt	m.p. (°C)	^{1}H-NMR
79	CH_3, CH_3, CH_3, CH_3-C(=O)-C(=O)-	free	237 ~ 238	(DMSO-d_6) δ : 1.52 (9H, s), 1.96 (3H, s), 2.04 (3H, s), 2.34 (3H, s), 4.58 (2H, d, J=6Hz), 7.46 (2H, d, J=10Hz), 7.72 (2H, d, J=10Hz)
80	CH_3, CH_3, CH_3-CH(-CH$_3$)-C(=O)-	free	189 ~ 190	(DMSO-d_6) δ : 1.30 (6H, d, J=7Hz), 2.00 (3H, s), 2.08 (3H, s), 2.38 (3H, s), 3.09 (1H, m), 4.52 (2H, d, J=6Hz), 7.50 (2H, d, J=10Hz), 7.74 (2H, d, J=10Hz)
81	CH_3, CH_3,	free	280 ~ 285	(DMSO-d_6) δ : 2.06 (3H, s), 2.12 (3H, s), 2.44 (6H, s), 4.62 (2H, s), 7.27 (2H, d, J=8Hz), 7.98 (2H, d, J=8Hz), 7.42 (2H, d, J=10Hz), 7.74 (2H, d, J=10Hz)
82	CH_3, CH_3, CH_3-N(-CH$_3$)-C(=O)-	hydrochloride	223 ~ 226	(DMSO-d_6) δ : 2.03 (3H, s), 2.12 (3H, s), 2.38 (3H, s), 2.92 (3H, s), 3.10 (3H, s), 4.81 (2H, s), 7.56 (2H, d, J=10Hz), 7.80 (2H, d, J=10Hz)
83	CH_3, CH_3-NH-C(=O)-	free	245 ~ 248	(DMSO-d_6) δ : 2.08 (3H, s), 2.34 (3H, s), 2.63 (3H, d, J=4.5Hz), 4.60 (2H, d, J=6Hz), 7.46 (2H, d, J=10Hz), 7.70 (2H, d, J=10Hz)
84	CH_3-CH_2-NH-C(=O)-	free	236 ~ 237	(DMSO-d_6) δ : 1.08 (3H, t, J=7Hz), 2.01 (3H, s), 2.08 (3H, s), 2.34 (3H, s), 3.04 (2H, q), 4.60 (2H, d, J=6Hz), 7.44 (2H, d, J=10Hz), 7.70 (2H, d, J=10Hz)

Example 23

Compounds shown in Table 9 were prepared by conducting the procedures described in Example 7 subsequent to the procedures described in Preparative Example 21.

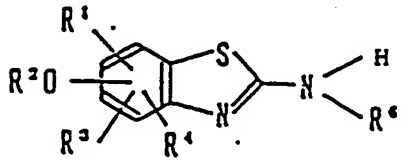
Table 9

Compd. No.		m.p. (°C)	^{1}H-NMR
85		199 ∿ 203	(DMSO-d_6) δ : 4.68 (2H, s). 7.36 (1H, s). 7.56 (2H, d, J=10Hz). 7.80 (2H, d, J=10Hz)
86		188 ∿ 190	(DMSO-d_6) δ : 4.64 (2H, s). 7.44 (2H, d, J=10Hz). 7.50 (1H, s). 7.72 (2H, d, J=10Hz)
87		142 ∿ 145 (dec.)	(DMSO-d_6) δ : 4.44 (2H, s). 6.50 (1H, s). 7.41 (2H, d, J=10Hz). 7.73 (2H, d, J=10Hz)

Claims

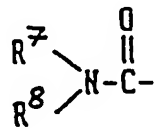
Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A benzothiazole compound having the below shown formula or a pharmacologically acceptable salt thereof:

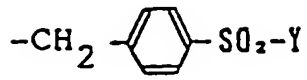


wherein R^1, R^3, and R^4 which may be the same or different are each a hydrogen atom, a straight-chain or branched alkyl group having 1 to 6 carbon atoms, a halogen atom, a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, an aroyl group selected from benzoyl, toluoyl and naphthoyl, a heteroaroyl group selected from furoyl, nicotinoyl and isonicotinoyl, a hydroxyl group, a straight-chain or branched alkoxy group having 1 to 6 carbon atoms, a hydroxy straight-chain or branched alkyl group having 1 to 6 carbon atoms, a nitro group, an amino group, or a dialkylamino group in which the alkyl groups are straight-chain or branched and have 1 to 6 carbon atoms, provided that any two of R^1, R^3 and R^4 may be combined together to form an aromatic ring which may consist of only carbon atoms or additionally contain a nitrogen atom,

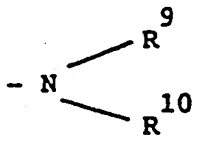
R^2 is a hydrogen atom, a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, an aroyl group selected from benzoyl, toluoyl and naphthoyl, a heteroaroyl group selected from furoyl, nicotinoyl and isonicotinoyl, or a group represented by the formula



wherein R^7 and R^8 which may be the same or different are each a hydrogen atom or a straight-chain or branched alkyl group having 1 to 6 carbon atoms, and R^6 is a group represented by the formula:



wherein Y is a straight-chain or branched alkyl group having 1 to 6 carbon atoms or a group represented by the formula



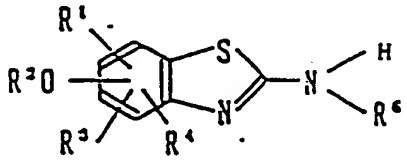
wherein R^9 and R^{10} which may be the same or different are each a hydrogen atom, a straight-chain or branched alkyl group having 1 to 6 carbon atoms, a straight-chain or branched alkoxy group having 1 to 6 carbon atoms or a hydroxy straight-chain or branched alkyl group having 1 to 6 carbon atoms.

2. A benzothiazole compound as claimed in claim 1 or a pharmacologically acceptable salt thereof, in which R^2 is hydrogen.

3. A benzothiazole compound as claimed in claim 1 or claim 2 or a pharmacologically acceptable salt thereof, in which R^1, R^3 and R^4 each represents a methyl group, R^2 represents a hydrogen atom and Y represents the group $-NH_2$.

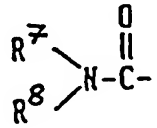
Claims for the following Contracting States : ES, GR

1. The use of a benzothiazole compound having the below shown formula or a pharmacologically acceptable salt thereof:



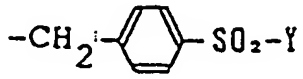
wherein R^1, R^3, and R^4 which may be the same or different are each a hydrogen atom, a straight-chain or branched alkyl group having 1 to 6 carbon atoms, a halogen atom, a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, an aroyl group selected from benzoyl, toluoyl and naphthoyl, a heteroaroyl group selected from furoyl, nicotinoyl and isonicotinoyl, a hydroxyl group, a straight-chain or branched alkoxy group having 1 to 6 carbon atoms, a hydroxy straight-chain or branched alkyl group having 1 to 6 carbon atoms, a nitro group, an amino group, or a dialkylamino group in which the alkyl groups are straight-chain or branched and have 1 to 6 carbon atoms, provided that any two of R^1, R^3 and R^4 may be combined together to form an aromatic ring which may consist of only carbon atoms or additionally contain a nitrogen atom,

R^2 is a hydrogen atom, a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, an aroyl group selected from benzoyl, toluoyl and naphthoyl, a heteroaroyl group selected from furoyl, nicotinoyl and isonicotinoyl, or a group represented by the formula

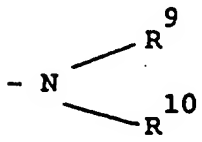


wherein R^7 and R^8 which may be the same or different are each a hydrogen atom or a straight-chain or

branched alkyl group having 1 to 6 carbon atoms, and R^6 is a group represented by the formula:



wherein y is a straight-chain or branched alkyl group having 1 to 6 carbon atoms or a group represented by the formula



wherein R^9 and R^{10} which may be the same or different are each a hydrogen atom, a straight-chain or branched alkyl group having 1 to 6 carbon atoms, a straight-chain or branched alkoxy group having 1 to 6 carbon atoms or a hydroxy straight-chain or branched alkyl group having 1 to 6 carbon atoms; for the manufacture of a medicament effective against allergy, asthma, affections of the skin, allergic rhinitis and affection of the cardiovascular system.

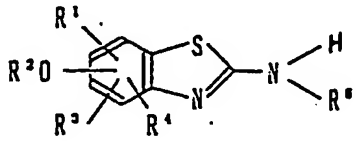
2. The use according to Claim 1, wherein R^2 is hydrogen.

3. The use according to Claim 1 or Claim 2, wherein R^1, R^3 and R^4 each represents a methyl group, R^2 represents a hydrogen atom and Y represents the group $-NH_2$.

Patentansprüche

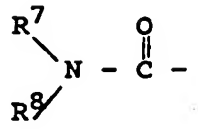
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Benzothiazol-verbindung, die die unten dargestellte Formel hat, oder ein pharmakologisch akzeptables Salz davon:

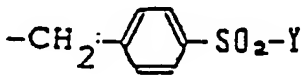


worin R^1, R^3 und R^4, die gleich oder verschieden sein können, jeweils darstellen ein Wasserstoffatom, eine geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, ein Halogenatom, eine geradkettige oder verzweigte Alkanoylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Aroylgruppe, ausgewählt aus Benzoyl, Toluoyl und Naphthoyl, eine Heteroaroylgruppe, ausgewählt aus Furoyl, Nicotinoyl und Isonicotinoyl, eine Hydroxylgruppe, eine geradkettige oder verzweigte Alkoxygruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Hydroxy-geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Nitrogruppe, eine Aminogruppe oder eine Dialkylaminogruppe, in der die Alkylgruppen geradkettig oder verzweigt sind und 1 bis 6 Kohlenstoffatome aufweisen, vorausgesetzt, daß zwei von R^1, R^3 und R^4 miteinander kombiniert werden können, um einen aromatischen Ring zu bilden, der nur aus Kohlenstoffatomen bestehen oder zusätzlich ein stickstoffatom enthalten kann,

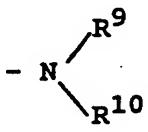
R^2 ein Wasserstoffatom, eine geradkettige oder verzweigte Alkanoylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Aroylgruppe, ausgewählt aus Benzoyl, Toluoyl und Naphthoyl, eine Heteroaroylgruppe, ausgewählt aus Furoyl, Nicotinoyl und Isonicotinoyl oder eine Gruppe der folgenden Formel



ist, in der
R^7 und R^8, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine geradkettige oder verzweigte Alkylgruppe, welche 1 bis 6 Kohlenstoffatome aufweist, sind und
R^5 eine Gruppe ist, die durch die folgende Formel dargestellt wird:



in der Y eine geradkettige oder verzweigte Alkylgruppe, welche 1 bis 6 Kohlenstoffatome aufweist, oder eine Gruppe, dargestellt durch die folgende Formel, ist



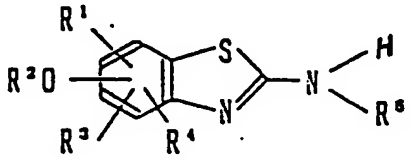
in der R^9 und R^{10}, die gleich oder verschieden sein können, ein Wasserstoffatom, eine geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine geradkettige oder verzweigte Alkoxygruppe, die 1 bis 6 Kohlenstoffatome aufweist, oder eine Hydroxy-geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, sind.

2. Benzothiazol-Verbindung nach Anspruch 1 oder ein pharmakologisch akzeptables Salz davon, in der R^2 Wasserstoff ist.

3. Benzothiazol-Verbindung nach Anspruch 1 oder Anspruch 2 oder ein pharmakologisch akzeptables Salz davon, in der R^1, R^3 und R^4 jeweils eine Methylgruppe darstellen, R^2 ein Wasserstoffatom darstellt und y die Gruppe $-NH_2$ darstellt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

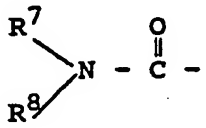
1. Verwendung einer Benzothiazol-Verbindung, die die unten dargestellte Formel hat, oder eines pharmakologisch akzeptablen Salzes davon:



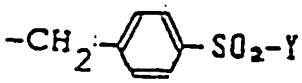
worin R^1, R^3 und R^4, die gleich oder verschieden sein können, jeweils darstellen ein Wasserstoffatom, eine geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, ein Halogenatom, eine geradkettige oder verzweigte Alkanoylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Aroylgruppe, ausgewählt aus Benzoyl, Toluoyl und Naphthoyl, eine Heteroaroylgruppe, ausgewählt aus Furoyl, Nicotinoyl und Isonicotinoyl, eine Hydroxylgruppe, eine geradkettige oder verzweigte Alkoxygruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Hydroxy-geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Nitrogruppe, eine Aminogruppe oder eine Dialkylaminogrup-

pe, in welcher die Alkylgruppen geradkettig oder verzweigt sind und 1 bis 6 Kohlenstoffatome haben, vorausgesetzt, daß zwei von R^1, R^3 und R^4 miteinander kombiniert werden können, um einen aromatischen Ring zu bilden, der nur aus Kohlenstoffatomen bestehen oder zusätzlich ein Stickstoffatom enthalten kann;

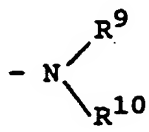
R^2 ein Wasserstoffatom ist, eine geradkettige oder verzweigte Alkanoylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, eine Aroylgruppe, ausgewählt aus Benzoyl, Toluoyl und Naphthoyl, eine Heteroaroylgruppe, ausgewählt aus Furoyl, Nicotinoyl und Isonicotinoyl oder eine Gruppe, dargestellt durch die Formel



in der R^7 und R^8, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, und
R^6 eine Gruppe ist, die durch folgende Formel dargestellt ist:



worin Y eine geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, oder eine Gruppe ist, die durch die Formel



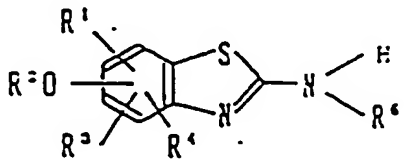
dargestellt wird, in der R^9 und R^3 und R^{10}, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom, eine geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, oder eine geradkettige oder verzweigte Alkoxygruppe, die 1 bis 6 Kohlenstoffatome aufweist, oder eine Hydroxy-geradkettige oder verzweigte Alkylgruppe, die 1 bis 6 Kohlenstoffatome aufweist, sind; zur Herstellung eines Medikaments, wirksam gegen Allergie, Asthma, Erkrankungen der Haut, allergische Rhinitis und Erkrankung des kardiovasulären Systems.

2. Verwendung nach Anspruch 1, wobei R^2 Wasserstoff ist.

3. Verwendung nach Anspruch 1 oder Anspruch 2, wobei R^1, R^3 und R^4 jeweils eine Methylgruppe darstellen, R^2 ein Wasserstoffatom darstellt und y die Gruppe $-NH_2$ darstellt.

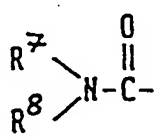
Revendications
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivé de benzothiazole répondant la formule donnée ci-dessous ou un sel pharmacologiquement acceptable de celui-ci :



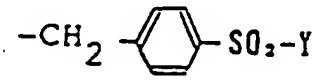
où R^1, R^3 et R^4, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un atome d'halogène, un groupe alcanoyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe aroyle choisi parmi les groupes benzoyle, toluoyle et naphtoyle, un groupe hétéroaroyle choisi parmi les groupes furoyle, nicotinoyle et isonicotinoyle, un groupe hydroxyle, un groupe alcoxy à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe hydroxyalkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe nitro, un groupe amino ou un groupe dialkylamino dont les groupes alkyle sont à chaîne droite ou ramifiée et ont 1 à 6 atomes de carbone, étant entendu que deux quelconques de R^1, R^3 et R^4 peuvent être combinés entre eux pour former un noyau aromatique qui peut être composé seulement d'atomes de carbone ou contenir de plus un atome d'azote,

R^2 est un atome d'hydrogène, un groupe alcanoyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe aroyle choisi parmi les groupes benzoyle, toluoyle et naphtoyle, un groupe hétéroaroyle choisi parmi les groupes furoyle, nicotinoyle et isonicotinoyle, ou un groupe représenté par la formule

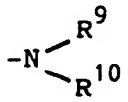


où R^7 et R^8, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, et

R^6 est un groupe représenté par la formule



où Y est un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone ou un groupe représenté par la formule



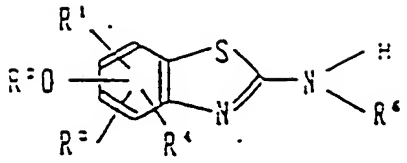
où R^9 et R^{10}, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe alcoxy à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone ou un groupe hydroxyalkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone.

2. Dérivé de benzothiazole selon la revendication 1, ou un sel pharmacologiquement acceptable de celui-ci, dans lequel R^2 est l'hydrogène.

3. Dérivé de benzothiazole selon la revendication 1 ou la revendication 2, ou un sel pharmacologiquement acceptable de celui-ci, dans lequel R^1, R^3 et R^4 représentent chacun un groupe méthyle, R^2 représente un atome d'hydrogène et Y représente le groupe $-NH_2$.

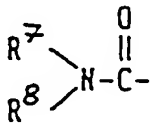
Revendications pour les Etats contractants suivants : ES, GR

1. Utilisation d'un dérivé de benzothiazole répondant à la formule donnée ci-dessous ou d'un sel pharmacologiquement acceptable de celui-ci :



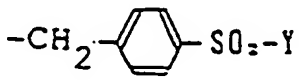
où R^1, R^3 et R^4, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un atome d'halogène, un groupe alcanoyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe aroyle choisi parmi les groupes benzoyle, toluoyle et naphtoyle, un groupe hétéroaroyle choisi parmi les groupes furoyle, nicotinoyle et isonicotinoyle, un groupe hydroxyle, un groupe alcoxy à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe hydroxyalkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe nitro, un groupe amino ou un groupe dialkylamino dont les groupes alkyle sont à chaîne droite ou ramifiée et ont 1 à 6 atomes de carbone, étant entendu que deux quelconques de R^1, R^3 et R^4 peuvent être combinés entre eux pour former un noyau aromatique qui peut être composé seulement d'atomes de carbone ou contenir de plus un atome d'azote,

R^2 est un atome d'hydrogène, un groupe alcanoyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe aroyle choisi parmi les groupes benzoyle, toluoyle et naphtoyle, un groupe hétéroaroyle choisi parmi les groupes furoyle, nicotinoyle et isonicotinoyle, ou un groupe représenté par la formule

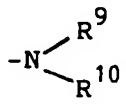


où R^7 et R^8, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, et

R^6 est un groupe représenté par la formule



où Y est un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone ou un groupe représenté par la formule



où R^9 et R^{10}, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, un groupe alcoxy à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone ou un groupe hydroxyalkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone ; pour la fabrication d'un médicament efficace contre l'allergie, l'asthme, des affections de la peau, la rhinite allergique et une affection du système cardio-vasculaire.

2. Utilisation selon la revendication 1, dans laquelle R^2 est l'hydrogène.

3. Utilisation selon la revendication 1 ou la revendication 2, dans laquelle R^1, R^3 et R^4 représentent chacun un groupe méthyle, R^2 représente un atome d'hydrogène et Y représente le groupe $-NH_2$.